

AMENDMENT

In the Claims:

Please cancel claims 69-88 as drawn to non-elected inventions.

RESPONSE

I. Second Restriction

The Second Restriction states "in response to Applicant's remarks filed on Paper NO. 10, 01/30/02, the restriction requirement sent in an earlier Official Action on Paper NO. 8, 05/02/01 is vacated and a new restriction requirement is issued below:" (Second Restriction at page 2).

Applicants are perplexed at this statement, given that Applicants' remarks in response to the first restriction requirement advocated that many of the seven groups set forth were not patentably distinct, and the corresponding claims should have been examined together. In response to Applicants' remarks concerning more unity, the Office has now taken the elected Group I invention and further restricted this into another eight allegedly distinct inventions.

Accordingly, Applicants respectfully request further clarification from the Office as to the reasons underlying the new restriction requirement and, in particular, which of Applicants' earlier remarks are believed to have prompted the new restriction.

The Second Restriction has determined that the claims of the former Group I invention are now drawn to eight further allegedly distinct inventions, set forth as:

Group I: Claims 1-18, **19, 21-35**, 36-37 and 40-68, apparently drawn to a composition comprising a first nucleic acid segment in association with a structural porous matrix, wherein the nucleic acid segment is a DNA molecule encoding a protein, and a method of making the composition, classified in class 435, subclass 320.1;

- Group II: Claims 1-18, **20**, 36-37, 40-68, apparently drawn to a composition comprising a first nucleic acid segment in association with a structural porous matrix, wherein the nucleic acid segment is an ANTISENSE molecule, and a method of making the composition, classified in class 435, subclass 320.1;
- Group III: Claims 38-39, apparently drawn to a composition, wherein the composition further comprises a cell population, and a method of making the composition, classified in class 435, subclass 325;
- Group IV: Claims 68-73, and 75-77, apparently drawn to a method for making genetically engineered cells *in vitro*, wherein the cells can be used in *ex vivo* gene therapy, classified in class 424, subclass 93.21;
- Group V: Claims 68-74, 78-82, 83, 84 and 88, apparently drawn to a method for stimulating bone progenitor cells located within a bone progenitor tissue site of an animal, classified in class 514, subclass 44;
- Group VI: Claims 68-74, 78-82 and 85, apparently drawn to a method for stimulating wound healing located within a wounded tissue site of an animal, classified in class 514, subclass 44;
- Group VII: Claims 68-74, 78-82 and 86, apparently drawn to a method for stimulating an immune response via targeting antigen presenting cells in an animal, classified in class 514, subclass 44; and
- Group VIII: Claims 68-74, 78-82 and 87, apparently drawn to a method for inducing cell death in a cell in an animal, classified in class 514, subclass 44.

II. Election

Applicants presently elect the Group I invention. This election is made with traverse as to the division between Groups I, II and III, but without traverse as to the division between Groups I-III and Groups IV-VIII. Applicants reserve the right to pursue any claims that remain withdrawn as directed to non-elected inventions in one or more divisionals or other applications claiming priority to the present and earlier priority applications.

Applicants also respectfully point out that many of original claims 89-101, canceled in response to the first restriction requirement, are now evidently unified with various of Groups IV-VIII set forth in the second restriction requirement. Applicants therefore reserve the

right to further traverse the differences between the first and second restriction requirements in future divisional or continuing applications claiming priority to the present application.

Applicants' traversal of the restriction between Groups I, II and III is based on the fact that the Office has not set forth two-way distinctness or sufficient reasons for insisting on restriction, the classification and field of search are essentially the same, there is no serious burden on the examiner should restriction not be maintained, and the presence of proper linking claims.

MPEP 806.05(c) states that a requirement for restriction must be supported by "both two-way distinctness and reasons for insisting on restriction", such as separate classification, status or field of search, separate particulars of patentability or combinations with distinct utility.

In terms of "classification and field of search", Applicants respectfully point out that each of the inventions set forth in Groups I-III are classified in the same class, and that two of the three are in the same class and subclass. The restriction requirement therefore contravenes MPEP 806.05(c).

MPEP 803 requires there to be a "serious burden" on the examiner should restriction not be made. "If the search and examination of an entire application can be made without serious burden, the examiner must examine it on the merits, even though it includes claims to independent or distinct inventions." Applicants submit that it would not constitute an undue burden for the claims to be examined together, particularly as unifying Groups II and III with Group I adds only three claims.

Applicants also respectfully invite attention to the linking claims present in the case. MPEP 809 states that, even with distinct inventions, "the linking claims must be examined with the invention elected, and should any linking claim be allowed, the restriction requirement must

be withdrawn." Any claims to non-elected inventions, even if previously canceled, must then be reinstated in the case. As the pending claims are intimately linked by a variety of generic and sub-generic linking claims, the claims should be maintained together, even if held to be distinct.

Accordingly, claims 20, 38 and 39, which are the only claims in Groups II and III, but not in Group I, are not being canceled but are maintained in the case until allowance of at least one linking claim.

III. Species Election Requirements and Responses

The Second Restriction sets forth a species election requirement. An initial election is first said to be required from claims 30-34, although this has actually been applied only to claims 30 and 31 (Second Restriction at page 6).

Applicants elect the species of at least a first nucleic acid segment that encodes a growth factor without traverse. Although the species election requirement appears to be confined to claims 30 and 31, in light of the Office's reference to claims 30-34, Applicants take the precaution of electing a sub-species of growth factor nucleic acids, wherein Applicants elect at least a first nucleic acid segment that encodes platelet derived growth factor.

IV. Status of the Claims

Prior to the Second Restriction, claims 1-88 were pending. Presently, the second Group I has been elected. Claims 69-88 have been cancelled as drawn to the non-elected inventions in Groups IV-VIII. Claims 20, 38 and 39, representing the inventions of Groups II and III, have been maintained in the case as unified with Group I. No claims of the Group I invention have been canceled or amended, and no new claims have been added.

As the elected claims encompass compositions comprising a structural matrix in association with at least a first and second nucleic acid segment, or a plurality of nucleic acid

segments (claims 36 and 37), no claims exclude the presence of at least a first nucleic acid segment that encodes a growth factor. Therefore, all claims read on the elected species. Claims 1-19, 21-24, 26-28 and 31-68 most directly read on the elected species. Any claims that the Office deems to be directed solely to originally non-elected species remain pending and are available for rejoinder in this application upon allowance of at least one generic or linking claim.

Claims 1-68 are therefore in the case. In accordance with 37 C.F.R. § 1.121, copies of the pending claims are attached hereto as **Exhibit A**. As no claims have been amended, another claim exhibit is not necessary.

V. Conclusion

This is a complete response to the Second Restriction Requirement. The response is timely filed on Monday, as the response was originally due on a Saturday. Should Examiner Kaushal have any questions, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,



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EXHIBIT A
PENDING CLAIMS
U.S. SERIAL NO. 09/442,542 (4100.002000; UM 1522p1)

1. A composition comprising at least a first nucleic acid segment in association with a structural matrix, wherein:
 - (a) at least a portion of said structural matrix is comprised of a porous polymer that contains pores formed by gas foaming and pores formed by leaching out of a particulate from the polymer; or
 - (b) at least a portion of said structural matrix is an alginate or modified alginate matrix.
2. The composition of claim 1, wherein at least a portion of said structural matrix is comprised of a porous polymer that contains pores formed by gas foaming and pores formed by leaching out of a particulate from the polymer.
3. The composition of claim 2, wherein at least a portion of said structural matrix is comprised of a porous polymer that has an open pore structure.
4. The composition of claim 3, wherein at least a portion of said structural matrix is comprised of a porous polymer that has an interconnected pore structure.
5. The composition of claim 2, wherein said structural matrix consists essentially of a porous polymer that has an open pore structure.
6. The composition of claim 2, wherein said structural matrix comprises at least a first matrix portion comprised of said porous polymer integrally connected to at least a second matrix portion comprised of an impermeable polymer.
7. The composition of claim 6, wherein said at least a first matrix portion is comprised of a porous polymeric material that has a substantially uniform open pore structure, and wherein said at least a second matrix portion is comprised of the same polymeric material in a form that lacks an open pore structure.
8. The composition of claim 2, wherein said structural matrix is a biocompatible matrix.

9. The composition of claim 2, wherein said structural matrix is a biodegradable matrix.
10. The composition of claim 2, wherein said structural matrix is a biocompatible and biodegradable matrix.
11. The composition of claim 2, wherein at least a portion of said structural matrix is comprised of a lactic acid polymer, glycolic acid polymer or lactic acid/glycolic acid copolymer matrix.
12. The composition of claim 11, wherein at least a portion of said structural matrix is comprised of a lactic acid/glycolic acid (PLGA) copolymer matrix.
13. The composition of claim 1, wherein at least a portion of said structural matrix is an alginate or modified alginate matrix.
14. The composition of claim 13, wherein at least a portion of said structural matrix is a modified alginate matrix that comprises at least one alginate chain section bonded to at least one molecule that mediates cellular interactions.
15. The composition of claim 14, wherein at least a portion of said structural matrix is a modified alginate matrix that comprises at least one alginate chain section bonded to at least one cellular interaction molecule selected from the group consisting of cell adhesion molecules, cell attachment peptides, proteoglycan attachment peptide sequences, proteoglycans, cell adhesion polysaccharides, growth factors and cell adhesion enzymes.
16. The composition of claim 15, wherein at least a portion of said structural matrix is a modified alginate matrix that comprises at least one alginate chain section bonded to at least one cellular interaction molecule selected from the group consisting of an RGD peptide, fibronectin, vitronectin, Laminin A, Laminin B1, Laminin B2, collagen 1 and thrombospondin.
17. The composition of claim 13, wherein at least a portion of said structural matrix is a modified alginate matrix prepared by a method comprising:
 - (a) providing a solution of a hydrogel-forming material and a surfactant;
 - (b) mixing said solution in the presence of a gas to form a stable foam;

- (c) exposing said stable foam to conditions or agents that result in gelling of the hydrogel-forming material and in the generation of gas bubbles therein; and
- (d) exposing the hydrogel containing gas bubbles to a vacuum to release the gas and form the hydrogel material having macroporous open pore porosity.

18. The composition of claim 13, wherein at least a portion of said structural matrix is a modified alginate matrix prepared by a method comprising:

- (a) providing a solution of a hydrogel-forming material, a surfactant and a gas-generating component, wherein said solution is capable of being mixed in the presence of a gas to incorporate the gas in the solution and form a stable foam;
- (b) mixing said solution in the presence of a gas to form a stable foam;
- (c) exposing said stable foam to conditions or agents that result in gelling of the hydrogel-forming material and to conditions or agents that result in generation of gas from the gas-generating component, to form a hydrogel containing gas bubbles therein; and
- (d) exposing said hydrogel containing gas bubbles therein to a vacuum to release the gas and to form the hydrogel material having macroporous open pore porosity.

19. The composition of claim 1, wherein said nucleic acid segment is a DNA molecule.

20. The composition of claim 1, wherein said nucleic acid segment is an antisense nucleic acid molecule or a ribozyme.

21. The composition of claim 1, wherein said nucleic acid segment is comprised within a plasmid or a recombinant expression vector.

22. The composition of claim 21, wherein said nucleic acid segment is operatively positioned downstream from a promoter within a recombinant viral expression vector.

23. The composition of claim 22, wherein said nucleic acid segment is operatively positioned downstream from a promoter within a recombinant adenovirus, a recombinant adeno-associated virus (AAV) or a recombinant retrovirus.

24. The composition of claim 21, wherein said nucleic acid segment encodes a protein or polypeptide.

25. The composition of claim 24, wherein said nucleic acid segment encodes a marker protein.

26. The composition of claim 24, wherein said nucleic acid segment encodes a protein or polypeptide that stimulates a bone progenitor cell when expressed in said cell.

27. The composition of claim 24, wherein said nucleic acid segment encodes a protein or polypeptide that stimulates a wound healing fibroblast, granulation tissue fibroblast or repair cell when expressed in said cell.

28. The composition of claim 24, wherein said nucleic acid segment encodes an antigenic or immunogenic protein or polypeptide that stimulates an immune response when expressed by an antigen presenting cell.

29. The composition of claim 24, wherein said nucleic acid segment encodes a cytotoxic or apoptosis-inducing protein or polypeptide that induces cell death upon expression in a cell.

30. The composition of claim 24, wherein said nucleic acid segment encodes a transcription or elongation factor, cell cycle control protein, kinase, phosphatase, DNA repair protein, oncogene, tumor suppressor, angiogenic protein, anti-angiogenic protein, immune response stimulating protein, cell surface receptor, accessory signaling molecule, transport protein, enzyme, anti-bacterial or anti-viral protein or polypeptide.

31. The composition of claim 24, wherein said nucleic acid segment encodes a hormone, neurotransmitter, growth factor, growth factor receptor, interferon, interleukin, chemokine, cytokine, colony stimulating factor or chemotactic factor protein or polypeptide.

32. The composition of claim 31, wherein said nucleic acid segment encodes a growth hormone (GH) protein or polypeptide, a parathyroid hormone (PTH) protein or polypeptide, a PTH1-34 polypeptide or a bone morphogenetic protein (BMP) protein or polypeptide.

33. The composition of claim 32, wherein said nucleic acid segment encodes a BMP-2A, BMP-2B, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7 or BMP-8 protein or polypeptide.

34. The composition of claim 31, wherein said nucleic acid segment encodes a transforming growth factor- α (TGF- α), TGF- β 1 or TGF- β 2 protein or polypeptide, a latent TGF β binding protein (LTBP) protein or polypeptide, an activin/inhibin protein or polypeptide, a fibroblast growth factor (FGF), a granulocyte/macrophage colony stimulating factor (GMCSF), an epidermal growth factor (EGF), a platelet derived growth factor (PDGF), an insulin-like growth factor (IGF) or a leukemia inhibitory factor (LIF).

35. The composition of claim 24, wherein said nucleic acid segment encodes a human protein or polypeptide.

36. The composition of claim 1, comprising at least a first and second nucleic acid segment.

37. The composition of claim 1, comprising a plurality of nucleic acid segments.

38. The composition of claim 1, further comprising a population of cells.

39. The composition of claim 38, wherein at least a portion of said nucleic acid segment is taken up by the cells comprised within said composition.

40. The composition of claim 1, prepared by admixing at least a first nucleic acid segment with said structural matrix.

41. The composition of claim 2, prepared by a process that comprises leaching out the particulate material from a composition comprising a gas foamed polymeric material, at least a first nucleic acid segment and a leachable particulate material.

42. The composition of claim 2, prepared by a process that comprises the steps of:

- (a) preparing an admixture comprising at least a first nucleic acid segment, particles capable of forming a polymeric structure and a leachable particulate material;
- (b) subjecting said admixture to a gas foaming process to create a porous polymeric structure that comprises said at least a first nucleic acid segment and said leachable particulate material; and

- (c) subjecting said porous polymeric structure to a leaching process that removes said leachable particulate material from said porous polymeric structure, thereby producing a polymeric structure of additional porosity that comprises said at least a first nucleic acid segment.

43. The composition of claim 42, wherein said admixture comprises said at least a first nucleic acid segment, beads or microspheres capable of forming a polymeric structure and said leachable particulate material.

44. The composition of claim 43, wherein said at least a first nucleic acid segment is incorporated within said beads or microspheres prior to said admixing or gas foaming steps.

45. The composition of claim 42, wherein said leaching process is conducted *in vitro* by subjecting said porous polymeric material to a leaching agent.

46. The composition of claim 42, wherein said leaching process is conducted *in vivo* by exposing said porous polymeric material to body fluids.

47. A composition comprising at least a first nucleic acid segment in non-covalent association with a structural matrix, wherein at least a portion of said structural matrix is comprised of a porous polymer that contains pores formed by gas foaming and pores formed by leaching out of a particulate from the polymer.

48. A composition comprising at least a first nucleic acid segment in non-covalent association with a structural alginate or modified alginate matrix.

49. A composition comprising at least a first nucleic acid segment in association with a structural matrix, said structural matrix comprising at least a first matrix portion comprised of a porous polymer that contains pores formed by gas foaming and pores formed by leaching out of a particulate from the polymer, wherein said first matrix portion is integrally connected to a second matrix portion comprised of an impermeable polymer.

50. The composition of claim 49, wherein said first and second matrix portions are comprised of the same polymeric material, separately fabricated to form a first, porous polymer having a uniform open pore structure and a second, impermeable polymer lacking an open pore structure.

51. The composition of claim 49, wherein said first and second matrix portions are comprised of different polymeric materials.

52. An admixture, comprising at least a first nucleic acid segment; beads or microspheres of a polymer capable of forming a gas-foamed polymeric structure; and a leachable particulate material.

53. The admixture of claim 52, wherein said at least a first nucleic acid segment is incorporated within said beads or microspheres.

54. A method for making a structural matrix-nucleic acid composition, comprising providing at least a first nucleic acid segment to a structural matrix, wherein at least a portion of said structural matrix is comprised of a porous polymer that contains pores formed by gas foaming and pores formed by leaching out of a particulate from the polymer.

55. The method of claim 54, comprising leaching out the particulate material from a composition comprising a gas foamed polymeric material, at least a first nucleic acid segment and a leachable particulate material.

56. The method of claim 55, comprising the steps of:

- (a) preparing an admixture comprising at least a first nucleic acid segment, particles of a polymeric material capable of forming a gas foamed polymeric structure and a leachable particulate material;
- (b) subjecting said admixture to a gas foaming process to create a porous polymeric structure that comprises said at least a first nucleic acid segment and said leachable particulate material; and
- (c) subjecting said porous polymeric structure to a leaching process that removes said leachable particulate material from said porous polymeric structure, thereby producing a polymeric structure of additional porosity that comprises said at least a first nucleic acid segment.

57. The method of claim 56, wherein said admixture is prepared by first incorporating said at least a first nucleic acid segment within said particles of a polymeric material and then admixing with said leachable particulate material.

58. The method of claim 57, wherein said admixture is prepared by first incorporating said at least a first nucleic acid segment within polymer beads or microspheres and then admixing with said leachable particulate material.

59. The method of claim 56, wherein the gas foaming process of step (b) comprises subjecting said admixture to an elevated pressure atmosphere of an inert gas in a manner effective to dissolve said gas into said polymeric material, and subjecting the gas-dissolved polymeric material to thermodynamic instability in a manner effective to cause nucleation and growth of gas pores sufficient to produce a continuous matrix of polymeric material that comprises said at least a first nucleic acid segment and said leachable particulate material.

60. The method of claim 59, wherein said thermodynamic instability is created by reducing said elevated pressure atmosphere.

61. The method of claim 56, wherein said leachable particulate material is a water-soluble leachable particulate material.

62. The method of claim 61, wherein said leachable particulate material is a salt, sugar or sugar alcohol.

63. The method of claim 62, wherein said leachable particulate material is NaCl, trehalose, glucose, sucrose or mannitol.

64. The method of claim 56, wherein said leaching process is conducted *in vitro* by contacting said porous polymeric material with a leaching agent.

65. The method of claim 56, wherein said leaching process is conducted *in vivo* by exposing said porous polymeric material to body fluids.

66. A kit comprising, in at least a first suitable container, at least a first nucleic acid segment and a structural matrix, wherein at least a portion of said structural matrix is a structural alginate or modified alginate matrix or a structural matrix comprised of a porous polymer that contains pores formed by gas foaming and pores formed by leaching out of a particulate from the polymer.

67. The kit of claim 66, wherein said at least a first nucleic acid segment and said structural matrix are physically associated within a single container.

68. An implantable device comprising at least a first nucleic acid segment in association with a structural matrix, wherein at least a portion of said structural matrix is a structural alginate or modified alginate matrix or a structural matrix comprised of a porous polymer that contains pores formed by gas foaming and pores formed by leaching out of a particulate from the polymer.